UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,075	07/24/2003	David M. Livingston	20363-019	3113

30623 7590 12/05/2006

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,075	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's reply dated 09/08/2006 has been received. Claims 5-7 and 11-49 have been cancelled. Claims 1 and 10 have been amended. Claims 1-4 and 8-10 are pending and under consideration in the instant office action.

Claim Objections

Claim 1 is objected to because of the following informalities: the term "Ang-2" at line 6 should be spelled out in full for the first occurrence of the term because multiple genes are represented by the abbreviation Ang-2. Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 5-7 and 10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. Claims 5-7 have been cancelled and claim 10 has been amended to depend from claim 8.

Claim Rejections - 35 USC § 112-1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1-4 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

Claim 1 lacks written description because in the instant case genera of Ang-2 regulatory elements that are capable of regulating gene expression are not set forth by the instant specification. Applicant is claiming a polynucleotide wherein the critical element of the invention is regulatory activity of a cis-acting element associated with the Ang-2 gene. The specification describes a specific 1220 nucleotide region upstream of the murine Ang-2 coding region that can drive Ang-2 gene expression in particular cell types both in vivo and in vitro. The specification fails to describe what DNA molecules fall into this genus and it was unknown as of Applicants' effective filing date that any of these DNA molecules other than that specifically set forth in the specification, would have the property of regulating gene expression. The claimed embodiments of Ang-2 regulatory elements encompassed within the genus lack a written description. There is no evidence on the record of a relationship between the structure of SEQ ID NO:1 taught by the specification that would provide any reliable information about the structure of DNA molecules within the genus. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction

to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of cis-acting Ang-2 regulatory elements. Therefore, only the regulatory region described in the specification, SEQ ID NO:1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that "to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention".

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Enablement

Claims 1-4 and 8-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide comprising (a) a first nucleic acid encoding a light-generating gene product operably linked to the Ang-2 regulatory region set forth in SEQ ID NO:1 and (b) a second nucleic acid encoding a selectable marker, wherein said selectable marker is operably linked to a promoter that, upon expression, allows for selection of cells comprising said polynucleotide in a eukaryotic host, does not reasonably provide enablement for use of the claimed nucleic acid wherein the Ang-2 regulatory region is not operably linked to the first nucleic acid, for use of any Ang-2 regulatory element, or for use of the polynucleotide wherein the second nucleic acid is not operably linked to a promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of

the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claim 1, as amended, is now limited to an isolated polynucleotide comprising an Ang-2 regulatory element. The specification teaches both promoter-driven and promoterless constructs (see page 11, line 16). The previous claim 1 was directed to a promoterless construct set forth by the specification that has a use that is different from that of the now claimed polynucleotide (i.e. the promoterless construct would be intended to use an endogenous promoter upon insertion into the genome; see Figure 3, for example; see also the luc-neo fusion gene as part of a pMMP viral vector, page 32, lines 8-9). Presently, upon amendment of the claims, the instantly claimed polynucleotide is distinct from that previously claimed with a different purpose and a different use. The instantly claimed polynucleotide uses the Ang-2 promoter, as taught by the specification to drive expression of the first nucleic acid (see page 30, lines 20-22), which was not originally claimed. The selectable marker gene in the construct containing the Ang-2 promoter, as taught by the specification, is operably linked to independent exogenous promoter. Thus, the all aspects of the basis of this rejection are necessitated by the amendment to claim 1.

The specification teaches generically an insertional vector comprising a tissue specific promoter operably linked to a gene encoding a light generating protein followed by a separate promoter driven selectable marker gene (page 11, lines 24-27; page 30, lines 20-22). The specification also teaches SEQ ID NO:1 as a sequence upstream of the Ang-2 coding region that is capable of driving expression of luciferase expression in mice (pages 33-34, Example 7) and in a number of different cell lines (page 34, lines 9-16). The claims, as generically written, however, fail to recite a relationship between the Ang-2 regulatory element and the gene encoding a light-generating gene product. The claim, thereby, encompasses placement of the Ang-2 element anywhere in the polynucleotide, including positions such that Ang-2 does not drive expression of the gene encoding a light generating gene product. The state of the art at the time of filing held that placement of a promoter is an important determinant for its activity,

perhaps more so than the overall sequence of the promoter [see Lewin, **Genes V**, 1994, at pages 847-849]. Thus, mere placement of a promoter in a vector with a gene of interest will not necessarily lead to expression of the gene of interest. The promoter must be placed appropriately with respect to the coding regions, in operable linkage, to cause gene expression.

The embodiment of the invention encompassing use of a tissue-specific (Ang-2) regulatory element to drive Ang-2 expression also requires a separate promoter to drive expression of a selectable marker in eukaryotic cells. The specification, with respect to this aspect of the invention, does not teach fusion of the selectable marker gene to the gene encoding a light-generating gene product and does not teach insertion such that the selectable marker uses an endogenous promoter. For this construct, the selection (the second nucleic acid) is used in selecting transformed ES cells while the light-generating gene (first nucleic acid) product is desired in other cell types, not in the ES cell (pages 29-30, Example 1; see Figure 4C), indicating separate and independent promoters for each coding nucleic acid. The claims fail to require that a promoter be operably linked to the selectable marker gene (second nucleic acid) and the specification fails to teach how to use the claimed construct comprising a gene encoding a light-generating product and Ang-2 regulatory element in addition to a selectable marker gene wherein the selectable marker gene is not operably linked to an independent exogenous promoter. As set forth above, expression of a gene requires operable linkage to a promoter. Thus, the instantly claimed polynucleotide is not enabled as claimed wherein there is no promoter operably linked to the second nucleic acid.

To the extent that the specification fails to provide any guidance or to describe elements within SEQ ID NO:1 that are responsible for regulating Ang-2 expression and, additionally, the specification and the art at the time of filing failed to teach any other Ang-2 regulatory elements, the specification is only enabling for use of SEQ ID NO:1 in its entirety, as an Ang-2 regulatory element, because it was unpredictable at the time of filing which sequences within SEQ ID NO:1 were responsible for directing Ang-2 expression. As set forth by Lewin (1994), a promoter contains short, cis-acting elements spread out

over a larger region with sequences between them, the sequence of such spacer DNA being unimportant (page 847, col. 2). Thus, given the large nucleic acid set forth by SEQ ID NO:1 without any characterization or identification of necessary elements and their characteristic spacing, it would require one of skill in the art an undue amount of experimentation to characterize the sequences within SEQ ID NO:1 such that one could use any other than SEQ ID NO:1 in its entirety to drive gene expression.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1) The rejection of claims 1-6 and 8-10 under 35 U.S.C. 102(a) as being anticipated by Zakhartchenko et al [September 2001, BioTechniques, 31:676-684] is withdrawn in light of Applicant's amendment to claim 1 requiring a cis-acting Ang-2 regulatory element.

2) The rejection of claims 1-5 and 7 under 35 U.S.C. 102(a) as being anticipated by Wilson et al. [March, 2002, IDS] is withdrawn in light of Applicant's amendment to claim 1 requiring a cis-acting Ang-2 regulatory element.

3) The rejection of claims 1-5 and 7 under 35 U.S.C. 102(b) as being anticipated by Terouanne et al. [2000, Molecular and Cellular Endocrinology, 160:39-49] is withdrawn in light of Applicant's amendment to claim 1 requiring a cis-acting Ang-2 regulatory element.

4) The rejection of claims 1-6 and 8-10 under 35 U.S.C. 102(b) as being anticipated by Levine et al. [1991, Gene, 108:167-174] is withdrawn in light of Applicant's amendment to claim 1 requiring a cis-acting Ang-2 regulatory element.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) The rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Zakhartchenko et al. in view of Yee et al [1987, PNAS, 84:5197-5201] is withdrawn in light of Applicant's the cancellation of the claim.

2) The rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Zakhartchenko et al. in view of Hwang et al [1997, Journal of Virology, 71:7128-7131] or Hu [2000, Pharmacol. Reviews, 52:493-511] is withdrawn in light of Applicant's the cancellation of the claim.

3) The rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Levine et al. in view of Hwang et al [1997, Journal of Virology, 71:7128-7131] or Hu [2000, Pharmacol. Reviews, 52:493-511] is withdrawn in light of Applicant's the cancellation of the claim.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632